METHODS FOR THE DETERMINATION AND ADJUSTMENT OF PROLACTIN DAILY RHYTHMS

RELATED APPLICATIONS

This application is a continuation-in-part of U.S. application Ser. No. 719,745 filed Jun. 24, 1991, now U.S. Pat. No. 5,344,832, in turn a continuation-in-part of Ser. No. 463,327, filed Jan. 10, 1990, now abandoned, which is a continuation-in-part of Ser. No. 192,332 filed May 10, 1988, now abandoned, all by Anthony H. Cincotta and Albert H. Meier.

FIELD OF THE INVENTION

This invention relates to a method for the reduction in a subject, vertebrate animal or human, of body fat stores, and reduction of at least one of insulin resistance, hyperinsulinemia, hyperlipidemia and hyperglycemia, and other metabolic diseases, especially those associated with Type II diabetes. In particular the present invention is directed to methods for: (i) normalizing the daily prolactin secretion cycles of a human or vertebrate animal; (ii) diagnosing aberrant daily prolactin secretion cycles of a human or vertebrate animal; and (iii) determining the appropriate adjustments that need to be made to normalize such aberrant prolactin secretion cycles. Such adjustments include the relatively short-term daily administration to the subject of at least one of a prolactin stimulator and/or a prolactin inhibitor at a predetermined time of day (if only one is administered) or at different predetermined times of day (if both are administered). This relatively short-term therapy results in the long-term adjustment of aberrant or abnormal prolactin secretion cycles so that they conform to or simulate normal prolactin secretion cycles. In turn, this adjustment results in reduction and control over an extended time period of one or more metabolic disorders or other disorders dependent (in whole or in part) on the phase of at least one circadian central neural oscillation (which is expressed by the daily prolactin secretion rhythm).

BACKGROUND OF THE INVENTION

Diabetes, one of the most insidious of the major diseases, can strike suddenly or lie undiagnosed for years while attacking the blood vessels and nerves. Diabetics, as a group, are more often afflicted with blindness, heart disease, stroke, kidney disease, hearing loss, gangrene and impotence, than the non-diabetic population. One third of all visits to physicians are occasioned by this disease and its complications, and diabetes and its complications are a leading cause of death in this country.

Diabetes adversely affects the way the body uses sugars and starches which, during digestion, are converted into glucose. Insulin, a hormone produced by the pancreas, makes the glucose available to the body's cells for energy. In muscle, adipose (fat) and connective tissues, insulin facilitates the entry of glucose into the cells by an action on the cell membranes. The ingested glucose is normally converted in the liver to CO_2 and H_2O (50%); to glycogen (5%) and to fat (30–40%), which is stored in fat depots. Fatty acids are circulated, returned to the liver and metabolized to ketone bodies for utilization by the tissues. The fatty acids are also metabolized by other organs, e.g., muscle. The net effect of insulin is to promote the storage and use of carbohydrates, protein and fat. Insulin deficiency is a common and serious pathologic condition in man. In Type I diabetes the pancreas produces little or no insulin, and insulin must be injected daily for the survival of the diabetic. In Type II diabetes the pancreas produces some insulin, but the amount of insulin is insufficient, or less than fully effective due to cellular resistance, or both. In either form there are wide-spread abnormalities, but the fundamental defects to which the abnormalities can be traced are (1) a reduced entry of glucose into various "peripheral" tissues and (2) an increased liberation of glucose into the circulation from the liver (increased hepatic glucogenesis). There is therefore an extracellular glucose excess and an intracellular glucose deficiency which has been called "starvation in the midst of plenty". There is also a decrease in the entry of amino acids into muscle and an increase in lipolysis. Thus, as a result of the diabetic condition, elevated levels of glucose in the blood, and prolonged high blood sugar are indicative of a condition which will cause blood vessel and nerve damage. It is believed that obesity, or excess fat deposits, may trigger the onset of diabetes by increasing cellular resistance to insulin. Prior to the onset of diabetes, the pancreas of an obese subject is taxed to produce additional insulin; but eventually, perhaps over several years, insulin productivity falls and diabetes results. Reduction of body fat can improve insulin production, and it is thought avoid cellular insensitivity to insulin.

The reduction of body fat stores on a long term, or permanent basis in domestic animals would obviously be of considerable economic benefit to man, particularly since animals supply a major portion of man's diet; and the animal fat may end up as de novo fat deposits in man, with resulting adverse effects on health. The reduction of body fat stores in man likewise would be of significant benefit, cosmetically and physiologically. Indeed, obesity and insulin resistance, the latter of which is generally accompanied by hyperinsulinemia or hyperglycemia or both, are hallmarks of Type II diabetes. Whereas controlled diet and exercise can produce modest results in the reduction of body fat deposits, no effective treatment has been found for controlling either hyperinsulinemia or insulin resistance. Hyperinsulinemia is a higher-than-normal level of insulin in the blood. Insulin resistance can be defined as a state in which a normal amount of insulin produces a subnormal biologic response. In insulin treated patients with diabetes, insulin resistance is considered to be present whenever the therapeutic dose of insulin exceeds the secretory rate of insulin in normal persons. Insulin resistance is also defined by higher-than-normal levels of insulin i.e., hyperinsulinemia—when present with normal or elevated levels of blood glucose. Despite decades of research on these serious health problems, the etiology of obesity and insulin resistance is unknown.

The principal unit of biological time measurement, the circadian or daily rhythm, is present at all levels of organization. Daily rhythms have been reported for many hormones inclusive of the adrenal steroids. e.g., the glucocorticosteroids, notably cortisol, and prolactin, a hormone secreted by the pituitary. In an early article, discussing the state-of-the-art at that time, it was reported that "Although correlations have been made between hormone rhythms and other rhythms, there is little direct evidence that the time of the daily presence or peak level of hormones has important physiological relevance." See *Temporal Synergism of Prolactin and Adrenal Steroids* by Albert H. Meier, General and Comparative Endocrinology. Supplement 3, 1972 Copyright 1972 by Academic Press, Inc. The article reports that the peak concentration of prolactin occurs at different times of day in lean and fat animals. The article then describes arian